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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,849	08/09/2000	Bruce L. Roberts	GAO116C	8453

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Deborah Duggan
Genzyme Corporation
15 Pleasant Street Connerter
PO Box 9322
Framingham, MA 01701-9322

EXAMINER	
ZEMAN, MARY K	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,849	ROBERTS ET AL.	
	Examiner	Art Unit	
	Mary K Zeman	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *14-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group I, claims 1-13 in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Applicant should update the serial number of the application that was converted to a provisional, that is listed in the first paragraph of the specification. It is currently listed by attorney docket number and/or non-provisional number.

Information Disclosure Statement

The IDS filed 7/31/2002 has been entered and considered. An initialed copy of the PTO-1449 is included with this action.

Specification

The disclosure is objected to because of the following informalities: page 21 contains an impermissible diagram, which should be made into a figure, and then canceled from page 21. MPEP 608.01: "The specification, including any claims, may contain chemical formulas and mathematical equations, but may not contain drawings or flow diagrams."

Further, while Applicant has provided a computer readable format, and paper copy of the sequence listing, no amendment to the specification has been made to add the SEQ ID NO:s to

the appropriate sequences in the specification. *Failure to make such amendments will render the reply non-responsive.*

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: in step (d) the term "polynucleotides motifs" should be "polynucleotide motifs" for grammatical consistency. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the preamble and step (d) of claim 1, the metes and bounds of the term "polynucleotide fragment of a gene" are unclear. How many nucleotides are required to be a fragment? Is a single nucleotide included? How much of a fragment identifies a gene? Must the fragment encode the entire antigen? The claim sets forth no definition, and no definition is apparent in the specification.

Further in claim 1, when "a (first or second) cell" is referred to, it would appear Applicant actually means a population of cells, and not a single cell. Clarification is requested.

In claim 1, step (b), It is unclear what the term "the antigen displayed by antigen presenting cells" refers to. Does it refer to the cells set forth in step (a)? The cells in step (a) are not necessarily antigen presenting cells- merely cells with MHC that express antigen. Does it refer to other, separate, unspecified APC's that are not related to the cells in step (a)? If so, where do these cells come from, and the phrase lacks antecedent basis in the claim. It is further not clear whether the APC must be the same type of cell recited in step (a), or whether they can

be any type of APC. If the cells *are* related to the cells recited in step (a), the claim is entirely unclear, and the further limitation of claim 4 does not make sense.

In step (d) of claim 1, it refers to "polynucleotide motifs". This is incorrect, as the step to which it refers [step (b)] discloses "polynucleotides encoding a peptide sequence motif". These concepts are not interchangeable. A polynucleotide motif and a polypeptide motif are not the same.

In the preamble and step (d) of claim 2, the metes and bounds of the term "fragment of one or more genes" are unclear. How many nucleotides are required to be a fragment? Is a single nucleotide included? How much of a fragment identifies a gene? How can a single fragment be of more than one gene? Must the fragment encode the entire antigen? The claim sets forth no definition, and no definition is apparent in the specification.

In claim 2, step (b) the use of parentheses renders the claim indefinite. It is unclear if the terms in the parenthetical expression are intended to be a limitation of the claim.

The term "representative" in claim 2 is a relative term which renders the claim indefinite. The term "representative" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how to determine whether an identified transcript is "representative" of a gene. The claim does not provide a threshold for such a designation, nor is it clearly denoted in the specification.

Further in claim 2, step (c), the term "encoding antigens recognized by immune effector; and" appears to be missing at least one word. It would appear the limitation should be "encoding antigens recognized by immune effector cells; and"

Further in claim 2, step (d) refers to "the first group of cells". The claim does not recite any groups of cells, but two separate groups of primers that are combined, and used to amplify. It is also unclear which "first" cells are being referred to: the immune effector cells in the preamble? The APC referred to as a source of primer sequences in step (a)?

Claims 6 and 9 recite atypical Markush-type language. Legally acceptable language includes "selected from the group consisting of A, B, C, and D."

The metes and bounds of claim 9 are unclear, as none of the cells recited in claims 1 or 2 are obtained from a patient or animal such that the limitations as to the source of the expressed

antigen make sense. These are also not further limiting, as the source of the antigen does not materially change the physical or chemical nature of the antigen.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-11, 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Levinson (USP 5,721,351).

The claims are drawn to methods of identifying polynucleotide sequences that encode antigens recognized by immune effector cells. The methods comprise using differential expression between MHC matched cells wherein one population expresses antigen, and the other does not, identifying differentially expressed sequences, and comparing them to known polypeptide motifs recognized by immune effector cells. The immune effector cells can be cytotoxic T Lymphocytes (CTL's) from a variety of origins, and can be polyclonal from one or more individuals. The CTL's can recognize antigens from neoplastic or tumor cells. The antigen presenting cell can be an intact or foster APC. Also, the full gene corresponding to the identified sequence can be further identified and/or isolated.

Levinson (USP 5,721,351) discloses methods of identifying polynucleotide sequences (and their corresponding genes) which encode antigens recognized by immune effector cells such as CTL's. Levinson uses techniques of differential expression to compare the cDNA profiles of cell populations which either express or do not express antigens (stimulated versus non-stimulated, normal versus abnormal, infected versus non-infected, transfected versus non-transfected.) (See column 6 lines 6-31, column 13 line 60 to column 34 line 5) For example, transgenic animals which express particular T cell receptors are pulsed with antigen, samples are taken from a site of lymphocyte infiltration (lymph node) and the gene expression profile is

compared to similar samples from non-pulsed animals (column 16). RNA or cDNA from the samples can be obtained, and used in the differential expression analysis. These analyses can include differential screening, subtractive hybridization, and differential display (columns 17-18). The differential display technique uses groups of primers to amplify differentially expressed sequences (column 18). Polynucleotides confirmed as being differentially expressed can be further characterized and identified as target or fingerprint genes (column 19). PCR can them be used to isolate full length cDNAs representing the full length gene (column 19). Levinson teaches that known amino acid sequences or peptide motifs can be used to guide the selection of PCR primers or oligonucleotides most likely to obtain sequences of interest (column 20 lines 27-30). As such, Levinson anticipated the above rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levinson as applied to claims 1, 3-11 and 13 above, in view of Kinzler.

Claim 2 is drawn to methods of identifying polynucleotide sequences that encode antigens recognized by immune effector cells. The methods comprise using differential expression between sequences amplified from two populations of cells using two populations of

primers, wherein the cells are MHC matched cells wherein one population expresses antigen, and the other does not, identifying differentially expressed sequences, and comparing them to known polypeptide motifs recognized by immune effector cells. Claim 2 specifically recites the use of SAGE sequence tags as part of one set of primers.

As set forth above, Levinson (USP 5,721,351) discloses methods of identifying polynucleotide sequences (and their corresponding genes) which encode antigens recognized by immune effector cells such as CTL's. Levinson uses techniques of differential expression to compare the cDNA profiles of cell populations which either express or do not express antigens (stimulated versus non-stimulated, normal versus abnormal, infected versus non-infected, transfected versus non-transfected.) (See column 6 lines 6-31, column 13 line 60 to column 34 line 5) For example, transgenic animals which express particular T cell receptors are pulsed with antigen, samples are taken from a site of lymphocyte infiltration (lymph node) and the gene expression profile is compared to similar samples from non-pulsed animals (column 16). RNA or cDNA from the samples can be obtained, and used in the differential expression analysis. These analyses can include differential display (columns 17-18). The differential display technique uses different groups of primers to amplify differentially expressed sequences (column 18). Polynucleotides confirmed as being differentially expressed can be further characterized and identified as target or fingerprint genes (column 19). PCR can then be used to isolate full length cDNAs representing the full length gene (column 19). Levinson teaches that known amino acid sequences or peptide motifs can be used to guide the selection of PCR primers or oligonucleotides most likely to obtain sequences of interest (column 20 lines 27-30).

Levinson does not specifically disclose the use of serial analysis of gene expression (SAGE) tags as one set of primers in the differential display method.

Kinzler et al. (USP 5,695,937) disclose the SAGE method of identification of differentially expressed sequence through the use of specific oligonucleotide primers. This technique allows for the analysis of a large number of gene transcripts to identify differential expression patterns. The SAGE technique also allows for the identification of specific mRNA or cDNA sequences, and the corresponding genes (summarized at column 3) using very short oligonucleotide probes. The SAGE technique allows for the reduction of amplification bias, which is a common problem in the analysis of differential expression patterns. The SAGE

technique is routinely used to study normal versus diseased cells, or normal versus abnormal cells. Kinzler et al specifically studied pancreatic cancer cells and normal pancreatic cells. (examples 1-3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the SAGE technique of Kinzler in the methods of Levinson. The primers generated by the SAGE technique would have been completely compatible with the methods of Levinson, as they are PCR primers, and Levinson discloses the use of PCR in the methods. One would have been motivated to utilize the SAGE technique in the methods of Levinson as the SAGE technique allows comparison of expression of numerous genes among tissues, or between pathologic tissue and its normal counterpart. This analysis is useful for identifying relevant genes, in a short period of time.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levinson as applied to claims 1, 3-11 and 13 above, in view of Zweerink.

Claim 12 provides the limitation that foster antigen presenting cells are used that lack an antigen processing system and express MHC free of bound peptides.

As set forth above, Levinson (USP 5,721,351) discloses methods of identifying polynucleotide sequences (and their corresponding genes) which encode antigens recognized by immune effector cells such as CTL's. Levinson uses techniques of differential expression to compare the cDNA profiles of cell populations which either express or do not express antigens (stimulated versus non-stimulated, normal versus abnormal, infected versus non-infected, transfected versus non-transfected. Transfected cells are a type of foster antigen presenting cell.) (See column 6 lines 6-31, column 13 line 60 to column 34 line 5) For example, transgenic animals which express particular T cell receptors are pulsed with antigen, samples are taken from a site of lymphocyte infiltration (lymph node) and the gene expression profile is compared to similar samples from non-pulsed animals (column 16). RNA or cDNA from the samples can be obtained, and used in the differential expression analysis. These analyses can include differential screening, subtractive hybridization, and differential display (columns 17-18). The differential display technique uses groups of primers to amplify differentially expressed sequences (column 18). Polynucleotides confirmed as being differentially expressed can be further characterized

and identified as target or fingerprint genes (column 19). PCR can them be used to isolate full length cDNAs representing the full length gene (column 19). Levinson teaches that known amino acid sequences or peptide motifs can be used to guide the selection of PCR primers or oligonucleotides most likely to obtain sequences of interest (column 20 lines 27-30).

Levinson does not specifically teach the use of foster antigen presenting cells which lack an antigen processing system.

Zweerink et al. (1993 Journal of Immunology 150:1763-1771) disclose foster antigen presenting cells which contain a mutation in the antigen processing pathway. These cells produce MHC which are free of bound peptides. When exogenous peptide is added, it binds to the "empty" MHC molecules on the surface of the cells, allowing for the control of what antigen is presented.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the foster antigen presenting cells of Zweerink et al in the methods of Levinson. One would have been motivated to use these cell types in order to control the type of antigen being presented to the immune effector cells, such that one can readily identify relevant differentially expressed genes.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 6,338,945 and US 6,306,640 are recent patents by one of the inventors: Nicolette.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (571) 272-0723.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (571) 272-0722.

The Official fax number for this Art Unit is: (703) 872-9306

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the TC1600 Receptionist whose telephone number is (703) 308-0196.

mkz
3/3/04

MARY K. ZEMAN
PRIMARY EXAMINER
1631